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Farshad Banouei*

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Research Article

Long-Term Effects of Covid-19 On Spermatogenesis: Findings from A Prospective Study

Farshad Banouei*

Urology resident, Urology & Nephrology Research centre, Hamedan University of Medical Sciences, Hamedan, Iran.

***Corresponding Author:** Farshad Banouei, Urology & Nephrology Research center, Hamedan University of Medical Sciences, Hamedan, Iran.

Received Date: August 22, 2023; **Accepted Date: September 25, 2023; Published Date: October 02, 2023**

Citation: Farshad Banouei (2023), Long-Term Effects of Covid-19 on Spermatogenesis: Findings from a Prospective Study, *Clinical Trials and Clinical Research;* 2(5): **DOI:** 10.31579/2834-5126/041

Abstract

Background: Since the introduction of the first case of Covid-19 disease, very wide signs and symptoms of this disease have been seen. In this study, we intended to investigate the effect of this disease on spermatogenesis as one of the most important of these complications.

Methods and Materials: This study involved 152 patients, who underwent semen tests to analyze sperm count, morphology, and sperm motility meticulously. The patients were enrolled in the study and reevaluated after a 3-years duration of infection to conduct subsequent semen tests.

Results: The average sperm count decreased in these patients. Prior to contracting Covid-19, the average motility rate was 84%. After contracting Covid-19, 8 cases (5%) experienced motility rates below 20%, 43 cases (28%) had rates between 20% and 40%, 17 cases (11%) ranged from 40% to 60%, 60 cases (39%) ranged from 60% to 80%, and 24 cases (15%) had rates exceeding 80%. The mean normal morphology before Covid-19 in these patients was 87%. After contracting Covid-19, 28 cases (18%) had morphology rates below 20%, 59 cases (38%) ranged from 20% to 40%, 31 cases (20%) ranged from 40% to 60%, 7 cases (4%) ranged from 60% to 80%, and 27 cases (17%) had rates exceeding 80%. These findings indicate significant changes following Covid-19 infection.

Conclusion: By utilizing the findings from this study and other similar studies, it is crucial to strive towards a deeper understanding of the pathogenic mechanisms of this global virus. This endeavor necessitates additional efforts and research to be conducted.

Keywords: spermatogenesis; covid-19; spermogram

Introduction:

On December 31, 2019, 27 cases of pneumonia with unknown etiology were identified in Wuhan City, Hubei province, China [1]. Covid-19 has been declared a global pandemic, affecting more than 2.5 million people worldwide, with over 170,000 reported deaths. To mitigate the spread of the disease, various preventive measures such as infection control, patient isolation, and social distancing have been implemented [2]. Covid-19 exhibits a variable timeline and clinical presentation involving different organs. The management of Covid-19 is based on the observed symptoms and organ dysfunction, and the time interval between recovery and the onset of new symptoms can vary [3].

On January 30, 2020, the World Health Organization (WHO) declared the outbreak of Covid-19 in China a Public Health Emergency of International Concern, posing a high risk to countries with vulnerable health systems. The emergency committee emphasized the importance of early detection, isolation, prompt treatment, and contact tracing as measures to interrupt the spread of Covid-19[4].

In response to the official announcement of the Covid-19 epidemic, China implemented comprehensive and coordinated approaches for infectious disease control. The Huanan Seafood Wholesale Market, believed to be the initial source of the novel coronavirus, was closed on January 1, 2020[5]. Prevention and control strategies have been continuously refined to adapt to the complex and evolving situations. Recent research has used a phase-adjusted SEIR model to estimate the epidemic trend in Wuhan, China [6].

Studies have provided insights into the transmission pathways of Covid-19 by analyzing trends and mitigation measures in the epicenters. Airborne transmission has been found to be highly contagious and a major factor in the spread of the disease. Mandating face coverings has proven to significantly reduce infections, while other measures like social distancing alone are inadequate for public protection. Sound scientific knowledge is crucial for effective decision-making in current and future public health pandemics [7].

The WHO declared the Covid-19 outbreak a public health emergency of international concern on January 30, 2020, and characterized it as a pandemic in March 2020. While there is currently no approved medication for Covid-19, prevention through measures such as hand hygiene, social distancing, and quarantine remains the most effective approach. Increasing testing capacity can help identify more positive cases in the community and reduce secondary infections through stricter quarantine rules [8]. Clinical features of Covid-19 include a dry cough, fever, diarrhea, vomiting, myalgia, and individuals with multiple comorbidities are at a higher risk of severe infection and may present with acute kidney injury and features of acute respiratory distress syndrome (ARDS) [9].

RT-PCR is a diagnostic test that uses nasal swab, tracheal aspirate or bronchoalveolar lavage (BAL) specimens. The primary, and preferred, method for diagnosis is the collection of upper respiratory samples via nasopharyngeal and oropharyngeal swabs. The use of bronchoscopy as a diagnostic method for COVID-19 is not recommended as the aerosol that is generated poses a substantial risk for both patients and healthcare staff. Bron-choscopy can be considered only for intubated patients when upper respiratory samples are neg- active and other diagnostic tools would significantly change the clinical management. However, bron-choscopy may be indicated when clinical and safety criteria are met and in the case of uncertain diagnosis.

RT-PCR is the preferred diagnostic test using nasal swabs or respiratory samples. Bronchoscopy is not recommended due to the risk of generating aerosols, except for intubated patients in cases where upper respiratory samples are negative and other diagnostic tools would significantly impact clinical management. However, bronchoscopy may be considered when clinical and safety criteria are met, and the diagnosis is uncertain [10].

The prolonged time spent at home, restrictions on socializing, and economic losses during the Covid-19 pandemic have resulted in increased levels of anxiety and depression among many individuals [11, 12].

The impact of Covid-19 on spermatogenesis, the process of sperm production, is still being studied. Initial research suggests that the virus may have the potential to affect male reproductive health. Covid-19 has been found in semen samples, indicating the possibility of viral replication in the testes. However, the prevalence and persistence of the virus in semen are not yet fully understood. Covid-19 can also indirectly disrupt spermatogenesis through illness, fever, inflammation, and certain medications used in treatment. More research is needed to fully understand the long-term consequences of Covid-19 on male fertility and reproductive health. Consulting healthcare professionals is advised for personalized information and guidance.

Method and Materials:

This clinical trial study involved 214 medical staff, including physicians and nurses, who were exposed to Covid-19 between March 2020 and June 2023. After providing thorough explanations, complete satisfaction was obtained from all patients. Subsequently, the Covid-19 PCR test was conducted to diagnose and determine the severity of the disease, following the guidelines outlined in the 7th edition of the New Coronavirus Pneumonia Prevention and Control Program published by the National Health Commission of China.

To briefly summarize, the mild type was characterized by malaise without positive chest radiologic findings, the moderate type exhibited common respiratory infection symptoms such as fever, cough, and positive chest radiologic changes. The severe type was identified by the presence of conditions such as dyspnea (respiratory rate ≥ 30 per minute), low finger oxygen saturation (≤93% at rest), low PaO2/FiO2 (≤ 300mmHg), or rapid deterioration of chest radiological abnormalities (>50% within 24-48 hours). The critical type was determined when patients experienced respiratory failure requiring mechanical ventilation, shock, or multiple organ dysfunctions.

At the time of sampling, 27 individuals with any symptoms were excluded from the study. The age range of the remaining patients was between 20 and 54 years, with a mean age of 37. After confirming the absence of clinical symptoms and obtaining negative PCR results, semen analysis was performed on the patients.

Semen Analysis

In this study, semen samples were analyzed to assess sperm count, morphology, and sperm motility. Patients exhibiting any abnormalities in these parameters were excluded from the study, resulting in the exclusion of 3 cases.

Out of the remaining 184 patients who were followed up for a period of 3 years, 152 patients developed Covid-19, 2 patients died due to Covid-19, and 30 patients did not develop Covid-19.

The study included the 152 patients who had recovered from Covid-19, and after 3 years of infection, they underwent semen re-testing to evaluate any changes.

All statistical analyses were conducted using GraphPad Prism 6.04 (San Diego, USA) and SPSS 27.0 (Chicago, IL, USA). Continuous variables were presented as means ± standard deviations (SD) or medians and interquartile ranges (IQR) as appropriate. Categorical variables were summarized as counts and percentages (%). The distribution of data was assessed using the Kolmogorov-Smirnov test. Statistical significance was defined as p-values < 0.05.

Results:

A total of 152 patients were included in this study, and all semen parameters were examined in these patients.

Volume: The average semen volume in these patients was 5 ± 0.7 cc, which decreased to 4 ± 0.3 cc after Covid-19 infection, indicating a significant change in volume (p=0.02).

Color and appearance: The color of semen in all samples was milky before infection, and there was not much change observed after infection.

Coagulation time: The mean coagulation time of the samples in patients before infection was 28 ± 9 minutes, and it remained the same after infection without any significant changes.

Total count: The average sperm count in these patients before Covid-19 infection was 256 ± 61 million. After infection, 69 cases (45%) experienced a decrease to less than 40 million, 27 cases (17%) had a count between 40 to 80 million, 35 cases (23%) had a count between 80 to 120 million, and 7 cases (6%) had a count exceeding 120 million. In 14 cases (9%), no change was observed. These findings indicate a significant decrease in sperm count after Covid-19 infection (Bar Chart 1).

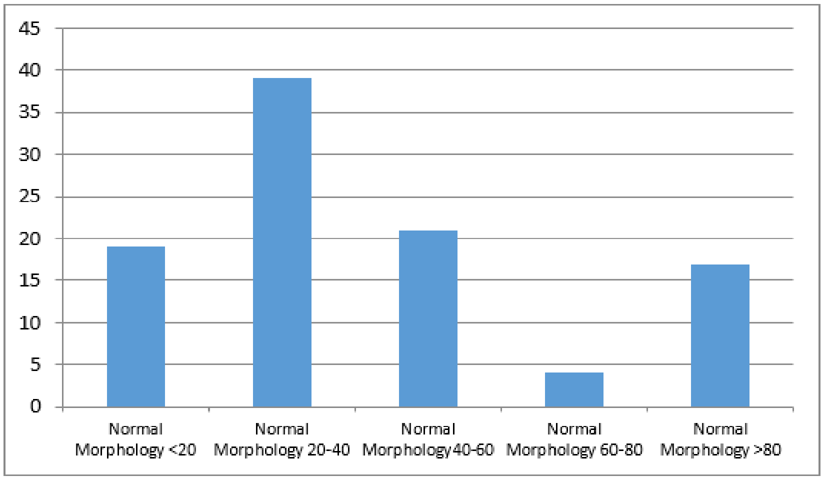

Figure 2: Total sperm count after Covid-19 infection.

Motility: In these patients, the average sperm motility before contracting Covid-19 was 84%. After getting Covid-19, 8 cases (5%) experienced a motility level below 20%, 43 cases (30%) had motility between 20% to 40%, 17 cases (11%) had motility between 40% to 60%, 60 cases (39%) had motility between 60% to 80%, and 24 cases (15%) had motility exceeding 80% (Bar Chart 2).

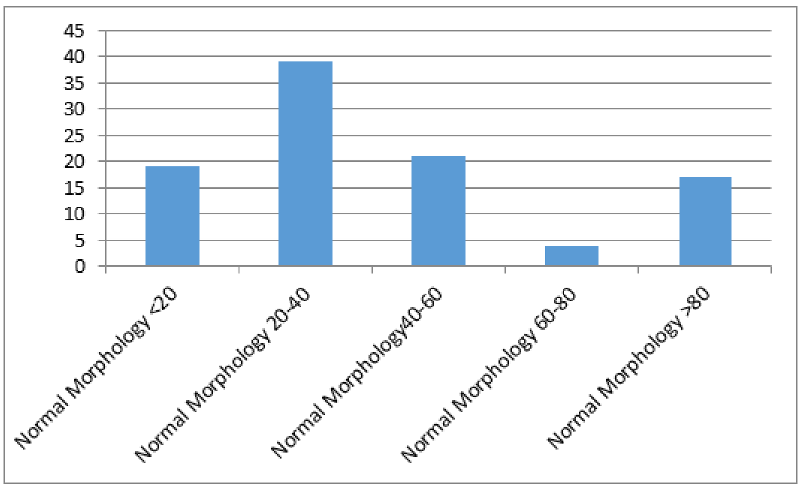

Figure 3: Sperm Motility after Covid-19 infection.

Normal morphology: The average normal morphology before Covid-19 in these patients was 87%. After Covid-19 infection, 28 cases (19%) exhibited a morphology level below 20%, 59 cases (39%) had morphology between 20% to 40%, 31 cases (21%) had morphology between 40% to 60%, 7 cases (4%) had morphology between 60% to 80%, and 27 cases (17%) had morphology exceeding 80%. These findings indicate significant changes in normal morphology following Covid-19 infection (Bar Chart 3).

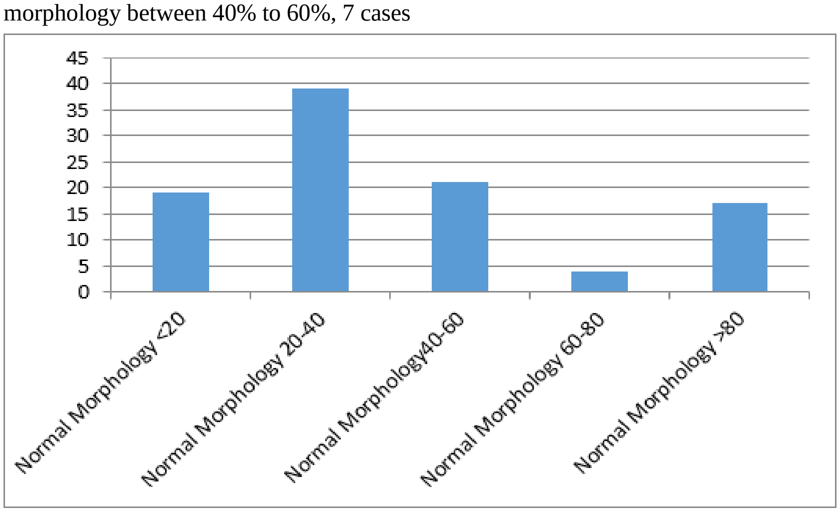

Figure 4: Sperm Morphology after Covid-19 infection.

PH: The pH range in these patients was 7.2 to 7.8, and it did not show significant changes after Covid-19 infection.

WBC and RBC: The mean number of white blood cells (WBCs) in semen for these patients was 8 before Covid-19, which increased to 13 after Covid-19 infection. The mean number of red blood cells (RBCs) was less than 2, and it did not exhibit significant changes after Covid-19 ($p<0.05$).

Discussion:

There is a growing body of evidence suggesting that the male reproductive system is susceptible to viral infections. Unlike bacterial infections that typically target accessory glands and the epididymis, viruses circulating in the bloodstream primarily affect the testes. Various virus families, such as the human immunodeficiency virus (HIV), mumps virus, influenza, Zika virus, and Coxsackie virus, have been found to cause orchitis and potentially lead to male infertility. [13]. Additionally, numerous viruses, including Ebola, HIV, Zika, and Hepatitis B/C viruses, have the ability to be transmitted through semen, leading to sexual transmission. The detrimental effects of these viruses involve direct harm to spermatozoa, disruption of normal sex hormone secretion, and dysregulation of inflammatory cytokines. For instance, research conducted on rams demonstrated that the bluetongue virus can replicate in endothelial cells located in the peritubular regions of the testes. This viral replication triggers an intensified type-I interferon response, reduced testosterone production by Leydig cells, and potential destruction of Sertoli cells. [14]. The testes primarily consist of seminiferous tubules and intertubular tissue. The seminiferous tubules play a vital role in sperm production, housing both spermatogonia (sperm-producing cells) and supportive Sertoli cells. Meanwhile, the interstitial Leydig cells, regulated by luteinizing hormone (LH), are responsible for testosterone synthesis [15].

Among various non-respiratory organs, the human testis exhibits high expression of ACE2. This leads to the query of potential reproductive consequences of COVID-19 in males, particularly in young men who have intentions of starting a family. The presence of ACE2 in the testis raises concerns regarding the possible adverse effects of the virus on male fertility. [16, 17].

Components of the renin-angiotensin-aldosterone system (RAAS) have been identified in both the testis and epididymis of humans and mammalian animal models. (15, 18-20). ACE2 expression in the testis is restricted to the Leydig and Sertoli cells in humans [21]. Nevertheless, unlike alveolar cells, it remains unclear whether cells engaged in spermatogenesis rely on intact ANG 1-7 (angiotensin 1-7) for their functional integrity. Exploring this aspect can be regarded as a fundamental inquiry within appropriate model systems. [22].

In the present study, the results indicated that there were no noticeable alterations in the volume, color, and pH of semen following Covid-19 infection. These findings suggest that the virus's impact on prostate-related factors may be minimal. This lack of effect could potentially be attributed to the absence of ACE (angiotensin-converting enzyme) as a predisposing factor for tissue damage in the prostate caused by Covid-19.

After Covid-19 infection, there was a significant decrease observed in both normal morphology and total sperm counts. These findings provide clear evidence of the impact of interleukins and leukotrienes on spermatogonia and the precursors of spermatogenesis. The decrease in normal morphology and total sperm counts suggests that the immune response mediated by these inflammatory factors has detrimental effects on the development and maturation of sperm cells. Further research can shed light on the specific mechanisms through which interleukins and leukotrienes exert their influence on spermatogenesis and potentially guide the development of targeted interventions to mitigate these adverse effects.

Conclusion: In light of the widespread prevalence of Covid-19 and its known as well as unknown side effects, there is an urgent need to comprehensively investigate and understand these effects. This knowledge is essential for preparedness in effectively managing and addressing the challenges posed by the virus. The findings from the present study, along with similar research endeavors, can contribute to this ongoing effort. It is crucial to recognize that uncovering the pathogenesis mechanisms of this global virus will require continuous and dedicated research endeavors. By advancing our understanding of Covid-19's pathogenesis, we can enhance our ability to mitigate its impact and develop targeted interventions. This necessitates collective and sustained efforts from the scientific community and further research initiatives.

Funding:

All costs of this study were paid by the researcher, and no financial support was received from any government or non-governmental entity.

Conflict of interest:

There is no conflict of interest in this study.

Acknowledgments:

We would like to thank all colleagues, especially the respected members of the psychiatry department who assisted us in conducting this research by providing their opinions.

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